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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/666,146	09/20/2000	Hilde Riethmuller-Winzen	PM 268411	5801

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EXAMINER
HUI, SAN MING R

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 04/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/666,146	Applicant(s) RIETHMULLER-WINZEN ET AL.	
	Examiner San-ming Hui	Art Unit 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *14-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 28-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The outstanding objection of claim 1 is withdrawn in view of the amendment filed January 18, 2002.

The outstanding rejections of claims 2, 3, 7, 8 and 9 set forth in the previous office action mailed July 18, 2001 under 35 USC 112, second paragraph is withdrawn in view of the amendment filed January 18, 2002.

The outstanding rejections of claims 1-13 under 35 USC 112, first paragraph are withdrawn in view of the applicant's remarks page 4-7 filed January 18, 2002.

The newly added claims 28-31 in amendment filed January 18, 2002 are acknowledged.

Claims 14-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention.

This application contains claims 14-27 drawn to an invention nonelected with traverse in Paper No. 8. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1-31 are pending.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-13 and 28-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Engel et al. (US Patent 5,663,145) in view of Hodgen (US Patent 5,658,884 from the Information Disclosure Statement received June 5, 2001) and Nachtigall et al. (Chapter 41, Danforth's Obstetrics and Gynecology, 1994, page 757-769), references of record in the previous office action mailed July 18, 2001.

Engel et al. teaches a method of administering the LHRH (GnRH) antagonist, cetrorelix, in two phases, to a patient in treatment of endometrial hyperplasia (See particular claim 14). Engel et al. also teaches that the dosage of cetrorelix useful in the method is 1 mg to 60 mg (See particular col. 3, line 8-9).

Engel et al. does not expressly teach the use of other agents herein in the method of treating endometrial hyperplasia. Engel et al. does not expressly teach the administration of the LHRH antagonist that cause the estrogen serum level to be 45-75 pg/ml, or 50-75 pg/ml. Engel et al. does not expressly teach the time and the frequency of administration of Cetrorelix. Engel et al. does not expressly teach the LHRH antagonist to be administered on cycle day one to three.

Hodgen teaches administration of GnRH (LHRH) antagonist in a method of treating endometriosis such that the estrogen level would be between 35 - 50 pg/ml (see particular col. 7, line 12-28; also col. 7, line 66 – col.8, line 4; also claims 9, 10, 12,13, 15, 16, 18, and 19).

Nachtigall et al. teaches that Danazol, an isoxazol derivative of 17-alpha-ethinyl testosterone, and oral contraceptives, non-steroidal anti-inflammatory, and analgesics

are useful in treating endometriosis (See particular page 765 – page 768, col. 1, 4th paragraph).

It would have been obvious for one of ordinary skill in the art at the time the invention was made to employing cetrorelix and other agents herein in a regimen herein to treat endometriosis.

One of ordinary skill in the art would have been motivated to employ cetrorelix and other agents herein in a regimen herein to treat endometriosis because all the agents herein are known individually to be useful in treating endometriosis. Therefore using the agents herein, in combination or alone, would have been reasonably expected to be useful in a method of treating endometriosis. It is *prima facie* obvious to combine agents each of which is taught by the prior art for the same purpose, in order to form a combination composition to be used for the very same purpose. *In re Kerhkoven* 205, USPQ 1069, 1072 (CCPA 1980). Furthermore, the optimization of result effect parameters (e.g., dosage range, dosing regimens) is obvious as being within the skill of the artisan.

It is applicant's burden to demonstrate unexpected results over the prior art. See MPEP 716.02, also 716.02 (a) - (g). Furthermore, the unexpected results should be demonstrated with evidence that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance. *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). Moreover, evidence as to any unexpected benefits must be "clear and convincing" *In re Lohr*, 137 USPQ 548 (CCPA 1963), and be of a scope reasonably commensurate with the scope of the subject matter claimed,

In re Linder, 173 USPQ 356 (CCPA 1972). In the instant case, the example disclosed in the specification at page 6 has been considered but are not found persuasive as to the presence of an unexpected result for the claimed invention over the cited prior art herein. This is because the example merely demonstrates that the LHRH antagonist is able to maintain a desirable estrogen level and provide the relief of symptoms associated with endometriosis. This is seen to be an expected effect based on the cited prior art. No comparison to the closest prior art is present. No convincing and clear unexpected result is seen.

Response to Arguments

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The combined teachings of the cited prior art taken as a whole clearly renders the claimed invention of treating endometriosis employing the actives herein obvious.

Applicant's arguments filed January 18, 2002 that one of ordinary skill in the art would not adjust the treatment regimen of LHRH antagonist taught in the prior art have been fully considered but are not persuasive because Hodgen et al. clearly provides the motivation to optimize the dose and/or regimen so that the desirable hypoestrogenic effects can be achieved (See Hodgen et al. col. 4, line 49-53). Hodgen et al. also teaches that the treatment period is up to 97 days (~13 weeks), which is close to the

dosing frequency of the claims herein. Hodgen et al. also teaches the LHRH antagonists can be administered periodically (See Hodgen et al. col. 5, line 38). The optimization of a dosage regimen for an active is considered within the skill of the artisan, absent evidence to the contrary. Moreover, according to MPEP 2144.05 III, applicants can rebut a *prima facie* case of obviousness by showing the criticality of a claimed range. However, no such evidence is seen to be present in the case.

Applicant asserts in the remarks filed January 18, 2002 that "it is well known in the art of therapeutical treatment of patients, that combining pharmaceutical agents can not be done freely, even if they are known for the same purpose" have been considered but are not found persuasive because contrary to applicant's assertion, it is well-known and routinely practiced in the pharmaceutical art to combine agents, which are known to be useful for the same purpose or condition individually, to treat the same medical condition. For example, Bactrim DS® is an antibiotic product that contains two antibiotics in one product. Moreover, it is known in the art that two or three agents may be administered together or separately to manage hypertension; for example, β-blockers plus diuretics or ACE inhibitors plus diuretics plus calcium channel blockers. Furthermore, this is the same for managing diabetes: metformin and sulfonylurea are known to be useful together in the diabetic treatment regimen. Further the law presumes that agents known for the same purpose individually are useful in a combination for the very same purpose. See *In re Kerkhoven* 205 USPQ 1069.

Applicant's remarks filed January 18, 2002 that oral contraceptives do not cure endometriosis have been considered but are not found persuasive as to the

nonobviousness of the claimed invention because even though oral contraceptives are not known to cure endometriosis, they clearly are known to treat endometriosis. In point of fact, endometriosis is currently known to be incurable, which in this aspect, the examiner agrees with the applicant. Therefore, combining oral contraceptives and LHRH antagonists, which are known to be useful to treat endometriosis individually into a single method useful for the very same purpose is prima facie obvious. See *In re Kerkhoven* 205 USPQ 1069. Additionally, no unexpected curative treatment effect for the claimed regimen over the cited prior art has been demonstrated. Further, the instant claims are not limited to a cure for diseases herein.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-

1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Minna Moezie, J.D., can be reached on (703) 308-4612. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

San-ming Hui
March 31, 2002

MINNA MOEZIE, J.D.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600